REMARKS

Introductory Comments:

Claims 1-32 were examined in the Office Action under reply and stand variously rejected under (1) 35 U.S.C. §112, second paragraph; (2) 35 U.S.C. §103(a); and (3) the judicially created doctrine of obviousness-type double patenting. These rejections are respectfully traversed as discussed more fully below.

Overview of the Above Amendments:

Claims 1, 2, 4, 5, 17, 18, 20 and 21 have been cancelled and claims 3, 6, 15, 16, 19, 22, 31 and 32 have been amended. In particular, claims 3 and 19 have been amended to recite the sequence of the NS3/4a antigen present in claims 6 and 22, respectively. These claims also recite that the antigen can have "at least 80% sequence identity to the contiguous amino acid sequence of SEQ ID NO:2." Additionally, claims 3 and 19 have been amended to clarify the relationship between the NS3/4a antigen and the conformational epitope. Claim 6 has been amended to recite that the NS3/4a antigen "consists of" the sequence of SEQ ID NO:2. Similarly, claim 22 has been amended to recite that the detectably labeled NS3/4a antigen "consists of" the detectable label and the sequence of SEQ ID NO:2. Claims 15, 16, 31 and 32 have been amended to claim the amino acid sequence with reference to the sequence identifiers. Finally, new claims 33 and 34 have been added and depend from claims 3 and 19, respectively. The new claims recite that the MEFA is MEFA 13 or MEFA 13.1.

Support for the above amendments can be found throughout the claims and specification as filed at, e.g., page 18, line 7; page 29, lines 14-15; and pages 36-37.

The foregoing amendments are made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to file one or more continuing applications containing the cancelled and/or unamended claims.

Rejections Under 35 U.S.C. §112, Second Paragraph:

Claims 1, 2, 3 and 6 were rejected under 35 U.S.C. §112, second paragraph as indefinite. The Office asserts: "It is not clear what applicant means by referring to either an 'isolated antigen' or a 'first region'." Office Action, page 2. In particular, the Office cites applicants' definition of isolated at page 18 of the specification but queries with respect to claim 1 "[i]n what way is the antigen isolated?" Office Action, page 2. Additionally, the Office asks whether the system uses multiple antigens or "is the claim indicating that an antigen can contain one or more antigenic epitopes?" Office Action, page 2. With respect to claim 3, the Office notes that an epitope as defined by the specification can include natural sequences up to 1,000 residues in length and states that this is contrary to the definition of "isolated" because "such a long polypeptide would have other epitopes in the adjacent regions." However, applicants submit the claims are indeed definite.

In particular, although the term "first region" is considered to be clear, this term no longer appears in the claims. Additionally, the Examiner has mischaracterized applicants' definition of "isolated." As explained at page 18 of the specification, the term "isolated" when referring to a polypeptide means that the molecule "is separate and discrete from the whole organism with which the molecule is found in nature **or** is present in the substantial absence of other biological macromolecules of the same type." (Emphasis added.) Thus, the definition of "isolated" is indeed consistent with its use in the claims. An isolated HCV antigen can have one, two, three, four, or even twenty or more epitopes, so long as the antigen does not include the entire HCV polyprotein as found in nature. Examples of this use of the term "isolated" can be found in claims of innumerable issued patents. Accordingly, contrary to the Office's assessment, the term is indeed definite. Nevertheless, as the subject method claims do not read on a naturally occurring system, the term has been removed. Thus, this basis for rejection has been overcome and withdrawal thereof is respectfully requested.

The Examiner also questions the definition of "epitope" presented in the application. The Examiner correctly recognizes that an applicant can be his or her own lexicographer but argues applicants have provided an "uncommon definition" that fails to put "one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term." Office Action, page 3. However, applicants respectfully disagree.

In particular, as recognized by the Examiner, a **specific definition** has indeed been provided in the application for the term "epitope." Thus, it is irrelevant that this definition is different than the two definitions of "epitope" supplied by the Examiner. Applicants are entitled to define the term as they please and have put the skilled artisan on notice regarding their definition of the term by virtue of the explicit definition found in the application.

Moreover, applicants disagree with the Office's view that the definition presented in the application is contrary to that understood in the art. As is readily known in the art, protein epitopes recognized by antibodies may be continuous or discontinuous depending on whether the amino acid residues forming the epitope are in continuous peptide linkage or are in spatial proximity to each other as a consequence of the tertiary or quaternary structure of the molecule. Discontinuous epitopes can include amino acids that are distant from one another in the amino acid chain. Thus, the epitope may spread over many more amino acids in the primary sequence than actually form the antibody binding site. See, for example, *Essential Immunology*, Ivan M. Roitt, Blackwell Scientific Publications, 1988, p. 56, Figure 4.3, showing a discontinuous epitope that spans the linear sequence of amino acids 83-145 of sperm whale myoglobulin.

Moreover, it is well known that although only a small part of the antigen surface may actually come in contact with antibody (e.g., 3 or 4 amino acid residues), for complex formation between the antigen and antibody to be possible, there must be complementarity between additional surface area of the antigen and the antibody. In some cases then, the entire surface of the antigen can be considered to contribute to binding ability and thus can be considered an "epitope." See, e.g., *Molecular Biology and Biotechnology, A Comprehensive Desk Reference*, ed. Robert A. Meyers, VCH Publishers, Inc., 1995, p. 455, appended for the Examiner's convenience. Thus, an antigen can include one or multiple epitopes, depending on the sequence of the antigen.

Based on the foregoing, it is evident that applicants' definition is not contrary to that understood in the art and even if it was, an explicit definition of the term appears in the application as filed.

Claims 3-32 were rejected for "using an incompatible combination of closed language in the independent claim followed by open claim language directed to the same term in dependent claims therefrom." Office Action, page 4. The Examiner considers the phrase in claim 1

"wherein the HCV antigens consist of one or more HCV NS3/4a conformational epitopes" to be inconsistent with language in dependant claims reciting that the conformational epitope "comprises an epitope from the NS3/4a protease region of the HCV polyprotein." Applicants have amended independent claims 3 and 19 to recite that the HCV NS3/4a antigen "comprises a conformational epitope." As explained at page 23, lines 15-17 of the application, the NS3 region includes the NS3 protease, found at positions 1027-1207, numbered relative to HCV-1, and the NS3 helicase, found at positions 1193-1711, numbered relative to HCV-1. Hence, an HCV NS3/4a antigen can "comprise" epitopes from either or both of these regions and the HCV antigen would still "consist of" an HCV NS3/4a antigen. Thus, the usage in the independent and dependent claims is indeed consistent and withdrawal of this basis for rejection is respectfully requested.

The Office further objects to claim 6 as unclear, arguing that the sequence claimed "is far greater than the length any one epitope within the region." Office Action, page 5. Thus, the Examiner states that he "is interpreting this as claiming a MEFA comprising SEQ ID NO:2." However, this interpretation is in error. First of all, a close reading of claim 6 shows that applicant is referring to the NS3/4a antigen recited in section (a) of claim 3, and not the epitope from the NS3/4a region present in the MEFA recited in section (c) of claim 3. Note that original section (a) of claim 3 recited an "HCV NS3/4a conformational epitope" as did claim 6. Nevertheless, applicants have amended claim 6 to refer to an "NS3/4a antigen." This language is consistent with the recitation found in section (a) of claim 3. Thus, this basis for rejection has also been overcome.

Similarly, the Office has objected to claim 1, arguing subpart (c) specifies the MEFA comprises at least one epitope from the same region of the HCV polyprotein as the one or more isolated antigens and that the MEFA must therefore include the same conformational epitope as the NS3/4a antigen. The Office argues this reasoning "is particularly applicable to claims such as claims 9 and 25 where the examiner can find little guidance as to the particular operability of such a construct." Office Action, pages 5-6, bridging paragraph. However, applicants disagree with this assessment.

In particular, as explained at page 30, lines 14-22 of the application, a number of epitopes from the NS3/4 region are known, including from the c33c, c200, c100 and 5-1-1 regions of

NS3/4. Examples of epitopes from these regions are given in Tables 2-5 of the application. For example, epitopes from c33c can be found within the amino acid sequence spanning positions 1211-1457 of the HCV polyprotein. Similarly, epitopes from 5-1-1 can be found within the amino acid sequence spanning positions 1689-1735 of the HCV polyprotein. The NS3/4a antigen of SEQ ID NO:2 corresponds to amino acid positions 1027-1711 of the HCV polyprotein (see, page 29, lines 14-17 of the application). Thus, it is evident this sequence includes various regions with epitopes that can react with antibodies in a sandwich assay that uses both the NS3/4a antigen and a MEFA as claimed, including the sequence found at the positions recited in claims 9 and 25. The claims have been amended to clarify this. Thus, it is not inconsistent that the MEFA does not contain the entire NS3/4a region and withdrawal of this basis for rejection is therefore requested.

The Examiner also requested applicants refer only to sequence identifiers in the claims. Applicants have so done.

Rejections Over the Art:

Claims 1-5, 7, 8, 10-14, 17-21, 23, 24 and 26-30 were rejected under 35 U.S.C. §103(a) as unpatentable over Chien et al., *J. Clin. Microbiol.* (1999) 37:1393-1397 ("Chien-1") in view of U.S. Patent No. 6,306,579 to Seidel et al. ("Seidel"). Claims 1-5, 7, 8, 10-14, 17-21, 23, 24 and 26-30 were also rejected under 35 U.S.C. §103(a) as unpatentable over U.S. Patent No. 6,428,792 to Valenzuela et al. ("Valenzuela") in view of Seidel. Claims 1-57, 8, 10-14, 17-21, 23, 24 and 26-30 were additionally rejected under 35 U.S.C. §103(a) as unpatentable over Chien et al., Proc. Natl. Acad. Sci. USA (1992) 89:10011-10015 ("Chien-2"). Applicants note that none of these rejections include claims 6 and 22, each of which recites the sequence of SEQ ID NO:2. This recitation has been added to independent claims 3 and 19, respectively. All claims either directly and ultimately depend from claims 3 and 19. Thus, these bases for rejection have been overcome and withdrawal thereof is respectfully requested.

Claims 15, 16, 31 and 32 were rejected under 35 U.S.C. §103(a) as unpatentable over Valenzuela in view of Seidel as applied to claims 1-5, 7, 8, 10-14, 17-21, 23, 24 and 26-30 "and further in view of Valenzuela et al. (U.S. Pat. No. 6,428,792) or (in the alternative further in view of Chien et al. (1999))." Office Action, page 10. Initially, applicants are confused by the

rejection as the only Valenzuela reference applied against claims 1-5, 7, 8, 10-14, 17-21, 23, 24 and 26-30 was the '792 patent. Clarification is therefore requested. However, applicants will respond to the rejection under the assumption that only one Valenzuela reference is being applied, namely, the '792 patent.

The Office argues both Valenzuela and Chien teach MEFA-6 and that Valenzuela also teaches MEFAs 3 and 5. The Office notes the arrangement of the epitopes in these MEFAs is different (presumably from the MEFAs recited in claims 15, 16, 31 and 32). However, the Office argues:

> One of ordinary skill in the art would have expected to produce a MEFA capable of detecting antibody specific to these antigenic epitopes/regions because Valenzuela teaches that these regions function in the context of a MEFA used in an immunological test even where their order has been rearranged.

Office Action, pages 10-11, bridging paragraph. However, applicants submit the combination of Valenzuela with Siedel and further in view of Chien-1 does not render the present claims obvious.

It is well settled that *prima facie* obviousness can only be established if the following three basic criteria are met: (1) there must be some suggestion or motivation to modify the reference(s); (2) there must be a reasonable expectation of success (for the modification and/or combination); and (3) the prior art reference(s) must teach or suggest all the claim limitations. MPEP §2143. Further, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on Applicant's disclosure. *In re Vaeck,* 20 USPQ2d 1438 (Fed. Cir. 1991). The Office has not satisfied these criteria.

Although Valenzuela and Chien-1 teach chimeric HCV polypeptides, none of Valenzuela, Chien-1 or Seidel, taken alone or in combination, teaches or suggests a sandwich-type assay using both a MEFA **and** an NS3/4a antigen comprising a conformational epitope and having the sequence of amino acids now specified in independent claim 3 (from which claims 15 and 16 depend) and claim 19 (from which claims 31 and 32 depend). Thus, the cited combination fails and withdrawal of this basis for rejection is respectfully requested.

Claims 6, 15, 16, 22, 31 and 32 were rejected under 35 U.S.C. §103(a) as unpatentable over PCT Publication No. WO 01/096870 to Chien et al. ("Chien-3") in view of Seidel. The

Examiner correctly observes that Chien does not teach the assay of the present invention but asserts the reference includes "identical amino acid sequences to that of the instant application." Office Action, page 11. The Examiner notes that Chien-3 has a common assignee and that the rejection may be overcome by an appropriate declaration regarding inventorship.

Accordingly, applicants are submitting a Declaration Regarding Inventorship ("the Declaration"), signed by the named inventors in the present application. The Declaration explains that Laura Tandeske, Carlos George-Nasciemento, Doris Coit and Angelica Medina-Selby, who are inventors on the PCT application along with David Chien and Phillip Arcanagel, are not also inventors of the particular assay methods claimed in the present application. Specifically, these inventors did not conceive of the idea of using the MEFAs and NS3/4a antigens described in the '870 PCT publication in the double antigen bridge assay claimed in the present application. Thus, applicants have made the showing sanctioned by *In re Katz*, 215 USPQ 14 (CCPA 1982) and MPEP 715.01(c), in order to remove this publication as a reference. Thus, this basis for rejection should be withdrawn.

The Obviousness-type Double Patenting Rejection:

Claims 1-30 were rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-20 of U.S. Patent No. 6,428,792. Applicants request this rejection be held in abeyance until claims in the present application are allowed. Applicants will then consider the propriety of filing a Terminal Disclaimer over the '792 patent.

CONCLUSION

Applicants respectfully submit that the claims define a patentable invention. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Please direct all further communications in this application to:

Marcella Lillis
Chiron Corporation
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097
Telephone: (510) 923-8406
Facsimile: (510) 655-3542.

Respectfully submitted,

Date: 11/15/04

By: _____
Roberta L. Robins
Registration No. 33,208
Attorney for Applicants

CHIRON CORPORATION
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097